

DEPRESSION OF TRANSMITTER RELEASE AND POSTJUNCTIONAL SENSITIVITY DURING NEUROMUSCULAR BLOCK PRODUCED BY ANTIBIOTICS

Y. N. SINGH, I. G. MARSHALL AND A. L. HARVEY

SUMMARY

In an attempt to elucidate the mechanisms by which antibiotics induce muscle paralysis, the effects of streptomycin, lincomycin, polymyxin B and clindamycin were investigated in the mouse phrenic nerve-hemidiaphragm preparation. Streptomycin resembled magnesium in reducing miniature endplate potential (m.e.p.p.) amplitude and frequency, whereas lincomycin, clindamycin and polymyxin B resembled tubocurarine in abolishing m.e.p.p. Endplate potential (e.p.p.) quantal content in streptomycin was 9, similar to that found in magnesium (5), whereas quantal contents in lincomycin (42), polymyxin B (37) and clindamycin (32) lay between values found in magnesium and in tubocurarine (123). Control quantal content was 152. In the presence of a mixture of magnesium and tubocurarine, no m.e.p.p. could be recorded and quantal content was 39. Blockade of twitches by a mixture of magnesium and tubocurarine was more successfully reversed by a mixture of calcium and neostigmine (to 70% of control) than by either calcium (to 49% of control) or by neostigmine (to 30% of control) alone. Lincomycin- and polymyxin B-induced blockades were poorly reversed by a mixture of the two reversal agents. It is concluded that streptomycin has a magnesium-like action whereas lincomycin, clindamycin and polymyxin B have relatively greater postjunctional and less prejunctional blocking activities. However, the effects of lincomycin and polymyxin B were not analogous to those of a tubocurarine-magnesium mixture, and their mechanism of action is still unclear. Clindamycin produced effects compatible with local anaesthetic activity.

Several classes of antibiotics, particularly the aminoglycosides (e.g. streptomycin, neomycin, kanamycin), tetracyclines, polymyxins, and lincomycin and clindamycin have been shown to produce skeletal muscle paralysis both in man and in experimental animals (Pittinger, Eryasa and Adamson, 1970; Pittinger and Adamson, 1972; Fogdall and Miller, 1974). The muscle paralysis produced by the aminoglycosides has been studied extensively both *in vivo* and *in vitro* and it has been proposed that the predominant mechanism of action is a magnesium-like depression of the evoked release of acetylcholine (Elmqvist and Josefsson, 1962; Vital Brazil and Prado-Franceschi, 1969; Wright and Collier, 1977; Singh, Harvey and Marshall, 1978; Singh, Marshall and Harvey, 1978), but there is evidence also of a component of postjunctional blocking activity (Vital Brazil and Corrado, 1957; Elmqvist and Josefsson, 1962; Singh, Harvey and Marshall, 1978; Singh, Marshall and Harvey, 1978). The neuromuscular block produced by the

aminoglycosides is reversed by calcium ions, suggesting that the aminoglycosides block transmitter release by inhibiting the influx of calcium ions into nerve terminals on nerve stimulation (Corrado, Ramos and de Escobar, 1959; Adams et al., 1976; Singh, Harvey and Marshall, 1978; Singh, Marshall and Harvey, 1978). The actions of the other classes of antibiotics that produce muscle paralysis have not been studied to the same extent as those of the aminoglycosides.

The site of action of several antibiotics (streptomycin, lincomycin, clindamycin and polymyxin B) has been investigated now by means of intracellular recording techniques. In these electrophysiological experiments, prejunctional actions were indicated by effects on the quantal content of endplate potentials (e.p.p.), which is a measure of the amount of acetylcholine released by a single nerve impulse. Changes in the frequency of the spontaneously-occurring miniature endplate potentials (m.e.p.p.) were taken also to indicate prejunctional actions. Postjunctional effects were indicated by effects on the amplitude of m.e.p.p. Thus, the results provide information on the effects of the antibiotics on transmitter release and on postjunctional receptor sensitivity. The antibiotics tested were compared with magnesium and with

Y. N. SINGH, M.Sc.; I. G. MARSHALL, Ph.D.; A. L. HARVEY, Ph.D.; Department of Physiology and Pharmacology, University of Strathclyde, George Street, Glasgow G1 1XW.
Correspondence to I. G. M.

tubocurarine as examples of drugs acting by predominantly prejunctional and postjunctional mechanisms respectively, and with a combination of magnesium and tubocurarine as a type of mixed pre- and postsynaptic blocking activity. Since the effects of lincomycin and of polymyxin B in the electrophysiological studies resembled those of a tubocurarine-magnesium mixture, the reversibility of the twitch depression produced by lincomycin and polymyxin B has been re-investigated using combinations of calcium and neostigmine.

METHODS

All experiments were performed on phrenic nerve-hemidiaphragm preparations from mice (Porton strain, 20–35 g).

Intracellular recording

Nerve-muscle preparations were pinned to the base of a 15-ml tissue bath through which Krebs-Henseleit (Krebs and Henseleit, 1932) solution was passed at a rate of 2.5–3 ml min⁻¹. The solution had previously been gassed with oxygen containing 5% carbon dioxide and was maintained at 30–32 °C.

The tissue bath was mounted on the stage of a binocular microscope (American Optics or Zeiss Jena Ergaval) fitted with a Leitz UM20/0.33 long-working-distance objective giving a magnification of approximately 300 times. E.p.p. and m.e.p.p. and membrane potentials were recorded with 2 mol litre⁻¹ potassium acetate-filled glass capillary microelectrodes (5–15 MΩ resistance). Signals were amplified by a WPI M701 electrometer and displayed simultaneously on Tektronix 5102 and 5103 oscilloscopes. The signals were recorded continuously on 35-mm film by a Grass oscilloscope camera. Single events were photographed from a storage oscilloscope on Polaroid film. Records were magnified by a film viewer and measured manually.

The endplate regions were localized by following nerve twigs and penetrating muscle fibres until spontaneous miniature endplate potentials (m.e.p.p.) with fast rise times (less than 1 ms) could be recorded. Control recordings of m.e.p.p. were made for at least 5 min from six different endplate regions before the administration of a drug.

The Krebs-Henseleit solution was replaced by an identical solution containing the antibiotic under study. The concentrations of antibiotics were chosen to produce abolition of twitching in response to nerve stimulation in 30–85 min. Once responses to nerve stimulation were below the threshold for muscle

contraction, several endplate regions were impaled and endplate potentials (e.p.p.) in response to nerve stimulation (0.2-ms pulses, 0.5 Hz frequency) and spontaneous m.e.p.p. were recorded.

To enable comparison between endplate regions with different resting membrane potentials e.p.p. and m.e.p.p. amplitudes were converted to a standard membrane potential of –70 mV and e.p.p. were corrected for non-linear summation (Hubbard, Llinas and Quastel, 1969). In each experimental situation, the intracellular recordings were obtained from six fibres in each muscle preparation. These values were averaged to produce a mean value for the muscle preparation. The mean values from six muscle preparations were then averaged to produce the quantal content values quoted in the table and text.

To obtain a measure of e.p.p. quantal content in the absence of drugs, muscles were immobilized by cutting the muscle fibres 1–2 mm on each side of the central band of endplate regions (Barstad and Lilleheil, 1968). E.p.p. quantal content was measured from responses to trains of impulses (70 Hz for 0.75 s). Under these conditions e.p.p. amplitude decreased during the first few impulses of the train and then was maintained at a fairly constant value. The quantal content of the last 30 e.p.p. in the train was calculated by the method of variance (del Castillo and Katz, 1954) and the quantal content of the first e.p.p. was then obtained by proportionality. In these experiments e.p.p. amplitudes were corrected to a standard membrane potential of –40 mV and were corrected for non-linear summation.

Twitch tension experiments

For twitch tension studies, mouse phrenic nerve-hemidiaphragm preparations were mounted in Krebs-Henseleit solution maintained at 32 °C and gassed with oxygen containing carbon dioxide (5%). Resting tension was approximately 0.5 g and contractions were recorded isometrically by Grass FTO3C force-displacement transducers connected to a Grass 7 polygraph. Blocking drugs were added for about 5–10 min to preparations that were stimulated via the phrenic nerve at a frequency of 0.1 Hz with rectangular pulses of 0.2 ms duration and of a strength greater than that necessary to elicit maximal twitches. To assess reversibility of muscle paralysis an 80–90% block was established and mixtures of calcium chloride to a final calcium concentration of 5 mmol litre⁻¹ or 10 mmol litre⁻¹ and neostigmine 1 µg ml⁻¹ (3 µmol litre⁻¹) were added. The extent of reversal was measured 5 min after addition of the reversal

mixture and the recovery values expressed as percentages of the control twitch height. All results quoted in the text and table, represent mean \pm standard error of six observations. Differences between means were analysed by non-paired Student's *t* test or by the Mann-Whitney *U* test. Values of $P < 0.05$ were regarded as statistically significant.

Drugs

Drugs used were tubocurarine chloride, streptomycin sulphate (both Sigma), polymyxin B sulphate (Wellcome), lincomycin hydrochloride and clindamycin hydrochloride (Upjohn).

RESULTS

Intracellular recording

In preparations in which muscle contraction in response to nerve stimulation was inhibited by tubocurarine $5 \mu\text{mol litre}^{-1}$ no m.e.p.p. could be recorded. E.p.p. varied only slightly in amplitude (fig. 1) and the e.p.p. quantal content of 123 ± 10 calculated by analysis of variance was not significantly different from the quantal content of 152 ± 17 obtained in the absence of drugs for the first e.p.p. in the train in cut hemidiaphragms.

In preparations paralysed by magnesium $19 \text{ mmol litre}^{-1}$, m.e.p.p. could still be recorded (fig. 2) although m.e.p.p. amplitude was $33 \pm 7\%$ lower than in control preparations (table I). E.p.p. amplitude fluctuated randomly with occasional failures (fig. 1). Quantal content of e.p.p. calculated by analysis of variance was 5 ± 0.5 . Neither tubocurarine nor magnesium produced any significant change in membrane potential.

At the concentrations tested, streptomycin, polymyxin B, lincomycin and clindamycin did not change membrane potential (table I).

In preparations paralysed by streptomycin $1.23 \text{ mmol litre}^{-1}$ m.e.p.p. of a reduced amplitude ($56 \pm 8\%$ lower than control) could be recorded (fig. 2, table I). As observed in magnesium-paralysed preparations, e.p.p. fluctuated randomly in amplitude, with some failures (fig. 1). Quantal content of e.p.p. in the presence of streptomycin $1.23 \text{ mmol litre}^{-1}$ was 9 ± 0.8 .

After neuromuscular block produced by polymyxin B $0.085 \text{ mmol litre}^{-1}$, lincomycin $4 \text{ mmol litre}^{-1}$ or clindamycin $0.7 \text{ mmol litre}^{-1}$ it was impossible to record m.e.p.p. The variation of e.p.p. amplitude was intermediate between that in tubocurarine and that in magnesium (fig. 1). E.p.p. quantal contents in the presence of these three antibiotics ranged from 32 to 42 (table I). A similar pattern was observed in preparations blocked by a mixture of postjunctionally-active and prejunctionally-active agents, that is tubocurarine $1.7 \mu\text{mol litre}^{-1}$ and magnesium $7 \text{ mmol litre}^{-1}$. In the presence of this mixture of agents, no m.e.p.p. could be recorded and e.p.p. quantal content was 39 ± 5 . However, in preparations blocked with clindamycin $0.7 \text{ mmol litre}^{-1}$, e.p.p. could be recorded in only some of the endplates penetrated. When endplates were penetrated before abolition of twitching, very small m.e.p.p. (around 15% of control amplitude) were recorded. M.e.p.p. frequency was increased to around 15 s^{-1} at this time. Thus, streptomycin appears to act mainly prejunctionally, whereas polymyxin B, lincomycin and clindamycin have mixed pre- and postjunctional blocking effects.

TABLE I. *M.e.p.p. amplitude, m.e.p.p. frequency, e.p.p. quantal content and membrane potential from endplates paralysed by antibiotics, magnesium and tubocurarine. †Significantly different ($P < 0.05$) from control; *significantly different ($P < 0.05$) from control and tubocurarine; ‡significantly different ($P < 0.05$) from magnesium and streptomycin; §obtained from cut muscle preparations; ¶concn in $\mu\text{mol litre}^{-1}$*

Treatment	Drug concn to produce neuromusc. block (mmol litre^{-1})¶	M.e.p.p.		E.p.p. (mean quantal content)	Membrane potential (mV)
		Amplitude (mV)	Frequency (Hz)		
Control	—	1.02 ± 0.03	1.50 ± 0.14	152 ± 17 §	72.9 ± 1.5
Tubocurarine	5¶	$0 \dagger \ddagger$	$0 \dagger \ddagger$	123 ± 10	73.7 ± 1.8
Magnesium	19	$0.67 \pm 0.06 \dagger$	$0.50 \pm 0.05 \dagger$	$5 \pm 0.5^*$	70.5 ± 1.1
Tubocurarine + magnesium	1.7 ¶ 7 }	$0 \dagger$	$0 \dagger$	$39 \pm 5^*$	72.2 ± 1.9
Streptomycin	1.23	$0.44 \pm 0.08 \dagger$	$0.60 \pm 0.08 \dagger$	$9 \pm 0.8^*$	71.8 ± 0.3
Polymyxin B	0.085	$0 \dagger \ddagger$	$0 \dagger \ddagger$	$37 \pm 4 \dagger^*$	75.5 ± 2.8
Lincomycin	4	$0 \dagger \ddagger$	$0 \dagger \ddagger$	$42 \pm 5 \dagger^*$	71.6 ± 1.1
Clindamycin	0.7	$0 \dagger \ddagger$	$0 \dagger \ddagger$	$32 \pm 8 \dagger^*$	71.4 ± 2.0

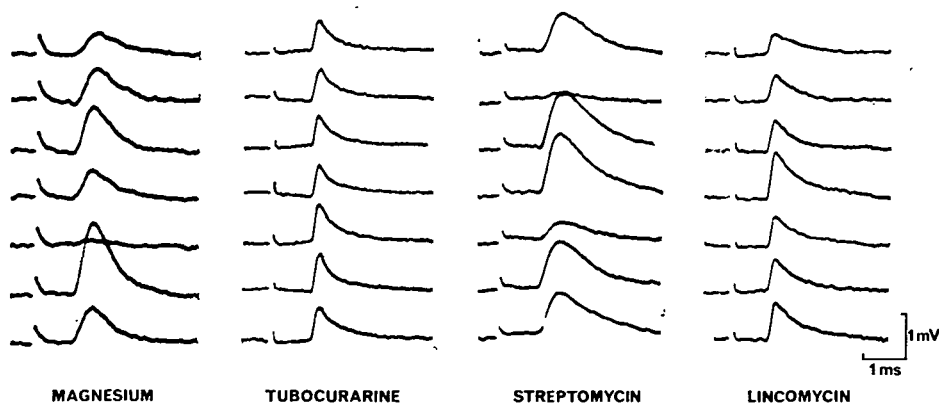


FIG. 1. Endplate potentials recorded intracellularly from mouse phrenic nerve-hemidiaphragm preparations after treatment with magnesium $19 \text{ mmol litre}^{-1}$, tubocurarine $5 \mu\text{mol litre}^{-1}$, streptomycin $1.23 \text{ mmol litre}^{-1}$ and lincomycin $4 \text{ mmol litre}^{-1}$. In each instance seven successive oscilloscope sweeps are represented. Note the variation in the height of e.p.p. recorded in magnesium whereas, in the presence of tubocurarine, e.p.p. amplitude did not vary markedly. The recordings in streptomycin were similar to those made in the presence of magnesium, whereas those in lincomycin were intermediate between recordings in magnesium and tubocurarine.

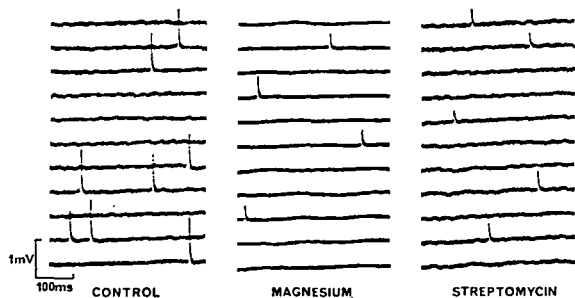


FIG. 2. Miniature endplate potentials recorded intracellularly from mouse phrenic nerve-hemidiaphragm preparations before and after treatment with magnesium $19 \text{ mmol litre}^{-1}$ and streptomycin $1.23 \text{ mmol litre}^{-1}$. Note that in magnesium and streptomycin m.e.p.p. of a slightly reduced amplitude and frequency were recorded. No m.e.p.p. could be recorded in the presence of tubocurarine $5 \mu\text{mol litre}^{-1}$, lincomycin $4 \text{ mmol litre}^{-1}$, polymyxin B $0.085 \text{ mmol litre}^{-1}$ or in a mixture of tubocurarine $1.7 \mu\text{mol litre}^{-1}$ and magnesium $7 \text{ mmol litre}^{-1}$.

Twitch tension studies

Results from intracellular recording studies indicated that lincomycin and polymyxin B produced effects quantitatively similar to the effect of a mixture of tubocurarine and magnesium. Tubocurarine blockade is reversed by neostigmine but not by calcium, and magnesium blockade is reversed by calcium but not by neostigmine, whereas the blockades produced by lincomycin and by polymyxin B were poorly reversible by calcium and neostigmine (Singh,

Harvey and Marshall, 1978). We have now studied the ability of a combination of neostigmine and calcium to reverse neuromuscular blockades produced by lincomycin, polymyxin B and a mixture of tubocurarine and magnesium.

A mixture of tubocurarine $2 \mu\text{mol litre}^{-1}$ and magnesium $8 \text{ mmol litre}^{-1}$ reduced twitch height to $11-16\%$ of control size in about 5-10 min. The resultant block was reversed to $30 \pm 5\%$ of control by doubling the calcium concentration of the bathing medium to $5 \text{ mmol litre}^{-1}$ and to $49 \pm 6\%$ of control by neostigmine $3 \mu\text{mol litre}^{-1}$. However, the block was reversed to $70 \pm 5\%$ of control by a mixture of calcium $5 \text{ mmol litre}^{-1}$ and neostigmine $3 \mu\text{mol litre}^{-1}$. Lincomycin-induced block ($2.6 \text{ mmol litre}^{-1}$) was reversed to $25 \pm 1\%$ of control by the mixture of calcium and neostigmine. Since calcium $5 \text{ mmol litre}^{-1}$ is almost totally ineffective against blockade induced by polymyxin B $0.3 \text{ mmol litre}^{-1}$ (Singh, Harvey and Marshall, 1978), a mixture of calcium $10 \text{ mmol litre}^{-1}$ and neostigmine $3 \mu\text{mol litre}^{-1}$ was tested. Although this mixture reversed polymyxin-induced block ($0.3 \text{ mmol litre}^{-1}$) to only $31 \pm 5\%$ of control, the reversal was poorly sustained, the block being re-established in 5-10 min.

DISCUSSION

Streptomycin, polymyxin B, lincomycin and clindamycin were compared with tubocurarine and magnesium as examples of reversible drugs acting

predominantly to block postjunctional acetylcholine receptors and prejunctional release of acetylcholine respectively. Thus, in preparations blocked by tubocurarine the quantal content of e.p.p. was great, indicating that tubocurarine had little effect on the amount of acetylcholine released by nerve impulses. In these preparations m.e.p.p. amplitude was reduced to zero, demonstrating the postjunctional blocking action of tubocurarine. In contrast, in preparations blocked by magnesium the quantal content of e.p.p. was very low and the frequency of m.e.p.p. was reduced; these findings indicate prejunctional actions of magnesium. Additionally, magnesium has some postjunctional blocking actions, as revealed by the reduction in m.e.p.p. amplitude.

As shown previously by other workers (Vital Brazil and Corrado, 1957), we have demonstrated that neuromuscular block produced by the aminoglycoside antibiotic streptomycin, like that produced by magnesium, was associated with depression of both evoked and spontaneous acetylcholine release and reduced postjunctional sensitivity. Small quantal contents have also been measured in the presence of other aminoglycoside antibiotics including neomycin (Elmqvist and Josefsson, 1962) and amikacin (Singh, Marshall and Harvey, 1978), and the aminoglycoside-like antibiotic spectinomycin (Singh, Marshall and Harvey, 1979).

Quantal contents in the presence of polymyxin B, lincomycin and clindamycin were lower than control values, indicating that reduction of transmitter output is a component of the compounds' actions. The depression of quantal content, however, was not as marked as the reduction seen in the presence of magnesium or streptomycin. Since m.e.p.p. activity was abolished, it can be concluded that polymyxin B, lincomycin and clindamycin also have postjunctional blocking effects. Our results demonstrate that polymyxin B, lincomycin and clindamycin have more prejunctional blocking activity than tubocurarine. Since tubocurarine has prejunctional blocking effects during repetitive nerve stimulation (Miyamoto, 1978) it is possible that the prejunctional effects of these three antibiotics will predominate during normal voluntary movement when the pattern of nerve impulses to skeletal muscle more closely resembles repetitive stimulation than low-frequency single shock stimulation.

A mixture of tubocurarine and magnesium possessed effects quantitatively similar to those of polymyxin B, lincomycin and clindamycin on e.p.p. quantal content and m.e.p.p., but the blockade of

twitches produced by the tubocurarine-magnesium mixture was reversed by a mixture of calcium and neostigmine whereas lincomycin- and polymyxin B-induced blockades were not reversed by calcium plus neostigmine. Thus, despite the superficial similarity of the effects of polymyxin B and of lincomycin to those of a magnesium-tubocurarine mixture, the mechanism of action of the antibiotics is not a simple combination of calcium- and anticholinesterase-reversible actions. Furthermore, although the effects of lincomycin and of polymyxin B on transmitter release and on postjunctional sensitivity are similar, the evidence presented is not sufficient to indicate that the two compounds share the same mechanisms. In fact, our previous studies have shown that concentrations of polymyxin B only slightly greater than those selectively blocking neuromuscular transmission have a depressant action on skeletal muscle contractility but no similar effect is seen with lincomycin (Singh, Harvey and Marshall, 1978).

The absence of e.p.p. activity immediately after muscle twitching was abolished by clindamycin probably indicates that the nerve terminals are no longer capable of conducting action potentials in the presence of the drug. A local anaesthetic activity of clindamycin has been described previously (Wright and Collier, 1976). The mixture of pre- and postjunctional blocking actions discussed above would be expected to contribute, along with the local anaesthetic action, to the muscle paralysing action of clindamycin. The increase in m.e.p.p. frequency before the abolition of m.e.p.p. activity has also been noted by Rubbo, Gergis and Sokoll (1977), but we have not analysed this effect in detail.

Our present results confirm that the aminoglycoside streptomycin acts primarily by a calcium-reversible prejunctional mechanism, whereas the other antibiotics tested act by different mechanisms. As the nature of the components of mixed pre- and postjunctional block produced by polymyxin B, lincomycin and clindamycin are as yet unknown, reversibility of these antibiotics by standard reversal agents remains difficult to predict and in the clinical situation it may be preferable to continue artificial ventilation until the return of spontaneous respiration.

ACKNOWLEDGEMENTS

The authors thank Wellcome Foundation Limited (for polymyxin B) and Upjohn Limited (for lincomycin and clindamycin). This study was supported by a project grant from the Medical Research Council and an equipment grant from the Smith, Kline and French Foundation.

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DEPRESSION DE LA SENSITIVITE
POST-JONCTION ET DU DEGAGEMENT
TRANSMETTEUR PENDANT LES BLOCAGES
NEUROMUSCULAIRES PRODUITS PAR
LES ANTIBIOTIQUES

RESUME

Au cours d'un essai qui a été fait pour élucider les mécanismes par lesquels les antibiotiques provoquent une paralysie des muscles, on a tout particulièrement étudié les effets de la streptomycine, de la lincomycine, de la polymyxine B et de la clindamycine sur une préparation nerf phrénique-demi-diaphragme d'une souris. La streptomycine a ressemblé au magnésium en réduisant l'amplitude et la fréquence du potentiel d'une plaque d'extrémité miniature (m.e.p.p.), alors que la lincomycine, la clindamycine et la polymyxine B ont ressemblé à la tubocurarine en abolissant le m.e.p.p. La teneur en quanta du potentiel de la plaque d'extrémité (e.p.p.) pour la streptomycine a été de 9, c'est-à-dire une valeur similaire à celle que l'on trouve dans le magnésium (5), alors que la teneur en quanta dans la lincomycine (42), la polymyxine B (37) et la clindamycine (32) se situe entre les valeurs trouvées dans le magnésium et dans la tubocurarine (123). La teneur témoin en quanta a été de 152. En présence d'un mélange de magnésium et de tubocurarine, il n'a pas été possible d'enregistrer le m.e.p.p. et la teneur en quanta a été de 39. Le blocage des crispations par un mélange de magnésium et de tubocurarine a été plus facilement inversé par un mélange de calcium et de néostigmine (à 70% des valeurs témoins) que par le calcium (à 49% des valeurs témoins) ou par la néostigmine (à 30% des valeurs témoins), seuls. Les blocages provoqués par la lincomycine et la polymyxine B ont été mal inversés par un mélange de deux agents d'inversion. On en a conclu que la streptomycine possède une action similaire à celle du magnésium alors que la lincomycine, la clindamycine et la polymyxine B ont des activités de blocage relatives moins pré-jonction et plus post-jonction. Cependant, les effets de la lincomycine et de la polymyxine B ne sont pas analogues à ceux d'un mélange de magnésium et de tubocurarine et leur mécanisme d'action n'est toujours pas clairement défini. La clindamycine a produit des effets compatibles avec l'activité anesthésiante locale.

UNTERDRÜCKUNG DER MITTLERSUBSTANZ
UND DER POSTJUNKTIONALEN SENSITIVITÄT
WÄHREND NEUROMUSKULÄRER
BLOCKIERUNG DURCH ANTIBIOTIKA

ZUSAMMENFASSUNG

Um den Mechanismus zu studieren, durch den Antibiotika Muskellähmung herbeiführen, wurden die Wirkungen von Streptomycin, Lincomycin, Polymyxin B und Clindamycin in einem Mäuse-Diaphragma-Nerven-Zwerchfellhälfte-Präparat untersucht. Streptomycin ähnelte Magnesium durch die Reduzierung von Schwingung und Frequenz des Miniatur-Endplattenpotentials (m.e.p.p.), während Lincomycin, Clindamycin und Polymyxin B wie Tubocurarin m.e.p.p. eliminierten. Der Quantengehalt von Endplattenpotential (e.p.p.) betrug in Streptomycin 9, ähnlich wie in Magnesium (5), wogegen die Werte in Lincomycin (42), Polymyxin B (37) und Clindamycin (32)

zwischen den in Magnesium und in Tubocurarin (123) gefundenen Werten lagen. Der Kontrollwert betrug 152. In Anwesenheit einer Mischung von Magnesium und Tubocurarin konnte kein m.e.p.p. festgestellt werden, und der Quantengehalt betrug 39. Die Zuckungsblockierung durch eine solche Mischung konnte erfolgreicher durch eine Mischung von Kalzium und Neostigmin aufgehoben werden (zu 70% des Kontrollwertes) als durch Kalzium (zu 49% des Kontrollwertes) oder durch Neostigmin (zu 30% des Kontrollwertes) allein. Blockierungen durch Lincomycin und Polymyxin B konnten nur schlecht durch eine Mischung dieser beiden Mittel aufgehoben werden. Daraus schliesst man, dass Streptomycin eine magnesiumartige Wirkung hat, während Lincomycin, Clindamycin und Polymyxin B eine relativ grössere postjunktionale und kleinere präjunktionale Wirkung haben. Allerdings waren die Wirkungen von Lincomycin und Polymyxin B nicht analog zu denen einer Tubocurarin-Magnesiummischung, und ihr Mechanismus ist noch immer nicht klar. Clindamycin produzierte Wirkungen, die mit Lokalanästhesie verträglich waren.

DEPRESION DE DESCARGA DEL TRANSMISOR Y SENSIBILIDAD POSTJUNCIONAL DURANTE BLOQUEO NEUROMUSCULAR CAUSADO POR ANTIBIOTICOS

SUMARIO

Con el objeto de descubrir los mecanismos mediante los cuales los antibióticos inducen parálisis muscular, se averiguaron los efectos de la estreptomycin, de la

lincomicina, de la polimixina B y de la clindamicina en la preparación hemidiafragma-nervio frénico del ratón. La estreptomycin se asemejaba al magnesio al reducir la amplitud y frecuencia del potencial de la placa terminal miniaturizada (p.p.t.m.), mientras que la lincomicina, la clindamicina y la polimixina B se parecían a la tubocurarina al eliminar el p.p.t.m. El contenido cuántico del potencial de la placa terminal (p.p.t.) en la estreptomycin era de 9, similar al que se encuentra en el magnesio (5), mientras que los contenidos cuánticos en la lincomicina (42), la polimixina B (37) y la clindamicina (32) se sitúan entre los valores encontrados en el magnesio y la tubocurarina (123). El contenido cuántico del control era de 152. En presencia de una mezcla de magnesio y de tubocurarina, no se pudo registrar ningún p.p.t.m. y el contenido cuántico era de 39. El bloqueo de las contracciones causado por una mezcla de magnesio y de tubocurarina pudo ser invertido con mayor éxito mediante una mezcla de calcio y de neoestigmina (hasta el 70% del control) que mediante el calcio solo (hasta el 49% del control) o la neoestigmina sola (hasta el 30% del control). La lincomicina y la polimixina B indujeron bloqueos cuya inversión por una mezcla de los dos agentes invertidores resultó bastante insatisfactoria. Se llega a la conclusión que la estreptomycin ejerce una acción parecida a la del magnesio, mientras que la lincomicina, la clindamicina y la polimixina B ejercen actividades bloqueadoras post-juncionales relativamente más fuertes, siendo las actividades pre-juncionales mucho menos marcadas. Sin embargo, los efectos de la lincomicina y de la polimixina B no fueron análogos a los de una mezcla de magnesio y de tubocurarina y no se aclaró todavía su mecanismo de acción. La clindamicina tuvo efectos compatibles con la actividad anestésica local.